NOTE: This disposition is nonprecedential.

# United States Court of Appeals for the Federal Circuit

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**ILLUMINA CAMBRIDGE LTD.,**
*Appellant*

**v.**

**INTELLIGENT BIO-SYSTEMS, INC.,**
*Appellee*

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2015-1123

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Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00128.

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**ILLUMINA CAMBRIDGE LTD.,**
*Appellant*

**v.**

**INTELLIGENT BIO-SYSTEMS, INC.,**
*Appellee*

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2015-1243

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Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00266.

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Decided: January 29, 2016

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WILLIAM R. ZIMMERMAN, Knobbe, Martens, Olson & Bear, LLP, Washington, DC, argued for appellant. Also represented by JONATHAN EDWARD BACHAND; BRENTON R. BABCOCK, Irvine, CA; NATHANAEL LUMAN, KERRY S. TAYLOR, San Diego, CA.

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Before LOURIE, BRYSON, and STOLL, *Circuit Judges.*

LOURIE, *Circuit Judge.*

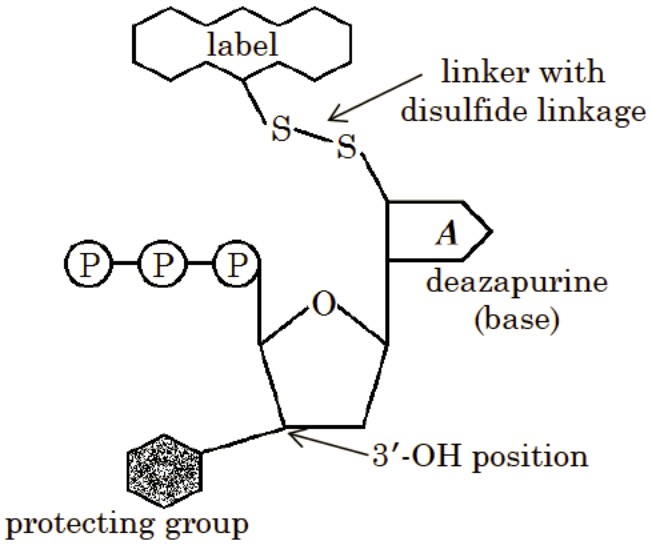
Illumina Cambridge Ltd. ("Illumina") appeals from the final written decisions of the United States Patent and Trademark Office, Patent Trial and Appeal Board ("the Board") cancelling all challenged claims of its U.S. Patents 7,057,026 ("the '026 patent") and 8,158,346 ("the '346 patent") and denying entry of substitute claims in two *inter partes* review proceedings. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, IPR2013-00128, Paper No. 92 (P.T.A.B. July 25, 2014); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, IPR2013-00266, Paper No. 73 (P.T.A.B. Oct. 28, 2014). Because the Board did not err in determining that Illumina failed to show that the proposed substitute claims are patentable over the prior art of record, and thus did not err in denying in part the motions to amend, we *affirm*.

## BACKGROUND

Illumina owns the '026 and '346 patents, which are both directed to DNA sequencing by synthesis ("SBS") with non-natural nucleotides. As the name implies, SBS allows one to determine the composition of a target DNA sequence by synthesizing new copies of the DNA. Briefly, the synthesis process involves splitting the double helix of a target DNA molecule into two strands and then incorporating complementary labeled nucleotides onto each strand to create two double helices. Non-natural nucleotides contain a non-natural base, *i.e.*, a modified purine or pyrimidine base.

The '026 patent is directed to nucleotide compositions of matter, while the '346 patent relates to methods of using such nucleotides. As the issues relating to the patentability of the claims of both of these patents are essentially the same, we evaluate both of them here in one opinion and decision.

An exemplary non-natural nucleotide of the two patents, pictured below, has a deoxyribose ring, with a protecting group attached at the 3′-OH position and a label connected to the non-natural base (here, deazapurine) by a linker (here, containing a disulfide linkage). According to the '026 and '346 patents, the linker and the protecting group for the claimed non-natural nucleotides are cleavable under identical conditions.




The claimed SBS methods involve incorporating the non-natural nucleotides into multiple copies of a target DNA molecule, one at a time for each strand in a stepwise fashion. At each step, the signal from the label is detected, indicating which nucleotide has been incorporated. Because a second nucleotide is added to the newly forming strand by its phosphate group binding to the 3′-OH position of a first nucleotide, a protecting group already attached at that position blocks the bond from being formed, and thus prevents multiple nucleotides from being added to the strand in the same step. Once the incorporated nucleotide is identified by the signal from its label, its attached protecting group is cleaved (or "deblocked"), allowing the next nucleotide to be incorporated. Ideally, the label is also cleaved at this time, clearing the slate for the next nucleotide's signal. This stepwise process repeats until the sequence of the target DNA molecule has been determined.

If a protecting group is not properly cleaved, then the newly forming strand will not incorporate the next complementary nucleotide in that step and will become "out of

phase" with the other strands, *i.e.*, its sequence will no longer match the others in any future steps. In contrast, if a linker for a label fails to be cleaved, the strand will still be in phase despite its incorrect or mixed signals; moreover, the linker will likely be cleaved, and the signal corrected, in subsequent cycles.

In 2012, a third party filed suit against Illumina, asserting several DNA sequencing patents for which Intelligent Bio-Systems, Inc. ("Intelligent Bio-Systems") is the exclusive licensee. In its answer, Illumina counterclaimed that Intelligent Bio-Systems infringed Illumina's '026 and '346 patents. Intelligent Bio-Systems then filed petitions for *inter partes* review at the Board, challenging claims 1–8 of the '026 patent and claims 1, 2, 4, 11, 12, 17, 18, and 19 of the '346 patent. The district court case was stayed pending resolution of these and several other related *inter partes* review proceedings.

The Board instituted review of both the '026 and '346 patents on the grounds of anticipation and obviousness. 2015-1123 Joint App. ("1123-J.A.") 332–350; 2015-1243 Joint App. ("1243-J.A.") 208–221. Instead of submitting responses to the institution decisions, Illumina filed motions to amend, requesting cancellation of all challenged claims of both patents, and entry of substitute claims 9–12 for the '026 patent ("'026-substitute claims"), 1123-J.A. 501–503, and claims 20–26 for the '346 patent ("'346-substitute claims"), 1243-J.A. 278–279. Noting that the cancellation requests were not contingent on the original claims being found unpatentable, the Board granted Illumina's motions in part, cancelling all of the challenged claims of both patents. 1123-J.A. 29–30; 1243-J.A. 23.

The Board then examined the proposed substitute claims for the '026 patent. Representative proposed substitute claim 9 for the '026 patent reads as follows, with Illumina's annotations for replacing claim 1:

> 9. A nucleotide triphosphate ~~or nucleoside~~ molecule, having a 7-deazapurine base that is linked to a detectable label via a cleavable linker, wherein the cleavable linker is attached to the 7-position of the 7-deazapurine base and wherein the cleavable linker contains a disulfide linkage, and wherein the nucleotide triphosphate molecule has a ribose or deoxyribose sugar moiety comprising a protecting group attached via the ~~2′ or~~ 3′ oxygen atom, and the disulfide linkage of the cleavable linker and the protecting group are cleavable under identical conditions.

1123-J.A. 30. The Board found only one new limitation that is different from the original claims: that the cleavable linker "contains a disulfide linkage." 1123-J.A. 30.

Starting with the premise that the obviousness of using a disulfide linkage was the main issue to be decided, the Board found that all of the claim limitations were described in the prior art. 1123-J.A. 37–39. The Board also found that the prior art provided a reason to use a disulfide linkage to attach a label to a base of a nucleotide, including for DNA sequencing, and with a reasonable expectation of success. 1123-J.A. 40–42. Because the proposed substitute claims do not require a disulfide linkage between the protecting group and the 3′-OH, the Board rejected Illumina's argument that the prior art's requirement of greater than 90% cleavage efficiency for a protecting group also applied to the claimed disulfide linkage. 1123-J.A. 42–44. Even so, the Board also found that one of skill in the art would have expected to achieve more than 90% cleavage efficiency of the disulfide bond by routine experimentation. 1123-J.A. 44–50. The Board determined that Illumina had not met its burden of showing that one of skill in the art would not have had a reasonable expectation of success, *viz.*, that identical conditions could not be selected in which the disulfide linkage is cleavable with less than 90% efficiency and the

protecting group is cleavable with greater than 90% efficiency.

The Board also rejected Illumina's proffered evidence of unexpected results of high cleavage efficiency of disulfide linkages. The Board found that Illumina did not provide a proper comparison to the closest prior art, and failed to provide evidence that the results were due to the claimed subject matter, not the experimental conditions or the latent properties of the bond. 1123-J.A. 52–54. The Board thus concluded that Illumina had not met its burden of showing that the proposed '026-substitute claims are patentable over the prior art of record. 1123-J.A. 54. The Board noted that such a showing is required in order to establish that the patent owner is entitled to the relief requested, *i.e.*, to amend the patent with the proposed substitute claims. 1123-J.A. 29, 31 (citing 35 U.S.C. § 316; 37 C.F.R. § 42.20(c)).

The Board separately also examined the proposed substitute claims for the '346 patent, which recite methods comprising providing, similarly, a nucleotide with a linker containing a disulfide linkage for attaching a label to the base, and removing the label and the protecting group from the nucleotide under a single set of chemical cleavage conditions. 1243-J.A. 23–24. The Board again found only one new limitation as compared to the original claims: that the cleavable linker "contains a disulfide linkage." 1243-J.A. 24. For virtually the same reasons as for the '026-substitute claims, the Board concluded that Illumina had not met its burden of showing that the proposed '346-substitute claims are patentable. 1243-J.A. 26–48.

The Board therefore denied in part Illumina's motions to amend both patents by entering the proposed substitute claims. Illumina timely appealed from the Board's final written decisions. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4).

## DISCUSSION

We review the Board's legal conclusions *de novo*, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), and the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). "Substantial evidence . . . means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 217 (1938).

Obviousness is a question of law based on underlying factual findings, including what a reference teaches and whether there would have been sufficient motivation to combine the prior art. *In re Baxter Int'l, Inc.*, 678 F.3d 1357, 1361 (Fed. Cir. 2012); *Rapoport v. Dement*, 254 F.3d 1053, 1060–61 (Fed. Cir. 2001); *In re Gartside*, 203 F.3d at 1316. For a motion to amend during an *inter partes* review proceeding, the patentee bears the burden of showing that its proposed substitute claims are patentable over the prior art of record. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1306–08 (Fed. Cir. 2015); *Prolitec, Inc. v. ScentAir Techs., Inc.*, 807 F.3d 1353, 1363–64 (Fed. Cir. 2015).

Illumina argues that the Board improperly limited its analysis to the disulfide linkage limitation, rather than also considering the *combination* of the additional limitations. Illumina contends that the '026-substitute claims added limitations of both (i) the linker containing a disulfide linkage and (ii) the disulfide linkage being cleavable under identical conditions as the protecting group. Similarly, the '346-substitute claims added limitations of both (i) the linker containing a disulfide linkage and (ii) the disulfide linkage and the protecting group being removed under a single set of chemical conditions. Although each limitation may have been independently disclosed in the prior art, Illumina asserts that the Board only found a motivation to use a linker with a disulfide linkage in SBS

methods, which was insufficient to find the full scope of the claimed subject matter obvious. Illumina reasons that because the prior art teaches both that SBS requires greater than 90% deblocking efficiency, and that cleaving disulfide linkages was variable and inefficient, one of skill in the art would not have been motivated to combine the prior art for SBS methods. Worse yet, Illumina argues, the Board improperly imposed a heightened standard of nonobviousness by requiring proof that it would have been *impossible* to combine the prior art to arrive at the substitute claims, *e.g.*, impossible to achieve higher cleavage efficiency yields for disulfide linkages. Illumina also asserts that the Board improperly discounted its evidence of unexpected results, which showed not simply high cleavage efficiency of the disulfide linkage, but *superior SBS results* using the claimed nucleotides.

Intelligent Bio-Systems responds that Illumina failed to carry its burden of showing that the proposed substitute claims were patentable over the prior art of record. Because the Board had already decided in its Decisions to Institute that the prior art taught all of the limitations in the original claims, Intelligent Bio-Systems contends, the only additional limitation in the proposed claims was the disulfide linker, and thus the Board only needed to address the prior art relating to the successful use of disulfide linkers in DNA sequencing. Intelligent Bio-Systems characterizes Illumina's arguments as using the variable cleavage efficiency of a disulfide linkage as a proxy for the greater than 90% cleavage efficiency of a protecting group required by the prior art; however, Intelligent Bio-Systems notes, the Board found that the claims do not require that they cleave at the same efficiency. Intelligent Bio-Systems also asserts that the Board did not err in finding that Illumina's evidence of unexpected results was insufficient to meet its burden of showing nonobviousness.

We agree with Intelligent Bio-Systems that the Board did not err in focusing on the prior art regarding disulfide linkages. For the proposed substitute claims in the context of *inter partes* review proceedings, Illumina bore the burden of proving patentability over the prior art of record; here, specifically, Illumina had to show that the substitute claims would not have been obvious in view of, *inter alia*, prior art raised during the review proceedings and prior art from the patent's original prosecution history. *See Prolitec v. ScentAir Techs.*, 807 F.3d at 1363–64. Because none of the original claims comprised the limitation of the linker containing a disulfide linkage, the Board chose to primarily address prior art relevant to that limitation to determine whether Illumina had proven that the addition rendered the claims as a whole nonobvious.

The Board did not analyze the obviousness of using a disulfide linkage in SBS in isolation, however; the original claims provided a backdrop for the Board to find that one of skill in the art would have reasonably expected to succeed in using a linker with a disulfide linkage as claimed. The prior art taught the use of linkers containing disulfide linkages for attaching a label to a nucleotide, as well as the desirability of simultaneously removing labels and protecting groups, in DNA sequencing methods. One of skill in the art would have been motivated to use a commercially available linker to attach a label to a nucleotide that also could be removed when removing the protecting group, and thus would have been motivated to modify SBS prior art with a disulfide linkage as claimed. The heightened standard that Illumina decries is instead properly Illumina's burden to show nonobviousness, proof that one of skill in the art would *not* have a reasonable expectation of success in using a disulfide linkage. Illumina simply failed to sufficiently elucidate grounds upon which the use of a disulfide linkage for SBS, particularly such a linkage cleavable under the same conditions as a

protecting group, would not have been obvious in view of the prior art.

Importantly, Illumina's arguments rely on the idea that one of skill in the art would not have used a linker with a disulfide linkage—for a desired combination in which the label and protecting group would be cleaved in identical conditions—because disulfide linkages did not appear to have sufficiently high cleavage efficiency to match the supposed minimum cleavage efficiency of protecting groups for SBS. The proposed substitute claims do not require that the linker and the protecting group be cleaved at the same efficiency rates, however, only that they are cleavable *under the same conditions*. The Board alluded to this by finding that Illumina had not met its burden to show that identical conditions could not have been selected; the implication being that nonobviousness might have been supported by evidence that one of skill in the art would not have expected there to be any set of conditions in which a disulfide linkage has lower cleavage efficiency than a protecting group and is still suitable for SBS.

Although Illumina provided an expert declaration stating that the prior art did not provide an expectation that disulfide cleavage conditions would cleave a protecting group with greater than 90% efficiency, the claims also do not require that the protecting group be cleaved at greater than 90% efficiency, much less that the linker also be cleaved at such efficiency. Nor do the claims limit the protecting group to one also involving a disulfide bond, which would inherently link its efficiency rate to the cleavage efficiency of the linker. We are not persuaded by Illumina's argument that one of skill in the art would not have been motivated to use a disulfide linkage as claimed, because the prior art does not expressly disclose greater than 90% cleavage efficiency of disulfide linkages.

Regardless, the Board found that even if that cleavage efficiency were required of the linker, Illumina had not met its burden to show that one of skill in the art would not have reasonably expected to achieve greater than 90% efficiency. The prior art taught that one of skill in the art could reasonably have expected to increase the cleavage efficiency of disulfide linkages by simple experimentation. Moreover, as the Board noted, it was not critical for the prior art to achieve higher cleavage efficiency of disulfide bonds. The lack of prior art disclosures of actually achieving higher efficiency yields does not render the teachings about increasing efficiency irrelevant; obviousness is not a question of novelty. *See EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) ("A reference must be considered for everything it *teaches* by way of technology and is not limited to the particular *invention* it is describing and attempting to protect."). Expert testimony in the record also supports the Board's finding that one of skill in the art would have reasonably expected to achieve increased efficiency for a disulfide linkage. Substantial evidence thus supports the Board's findings that several prior art references taught the additional limitations of the proposed substitute claims and that one of skill in the art would have had a reasonable expectation of success in combining the prior art to obtain the claimed invention.

The Board also did not err in finding that Illumina's evidence of unexpected results relative to the prior art was insufficient. Illumina failed to show that the unexpected results obtained were due to the claimed nucleotide rather than differences from the prior art, *e.g.*, the cleavage reagent used or other experimental conditions, or a latent property of the disulfide linkage. The Board therefore did not err in finding that Illumina had not met its burden to prove that the substitute claims were patentable over the prior art.

## CONCLUSION

We have considered the remaining arguments and conclude that they are without merit. Because substantial evidence supports the Board's determination that Illumina failed to meet its burden in showing that the proposed substitute claims in both patents are patentable over the prior art of record, we affirm.

**AFFIRMED**